

REMARKS

Claims 1-25 were pending in the application.. Claims 1-12 have been canceled without prejudice as being drawn to a non-elected invention. Claims 13, 16, 17, 19-21, 24, and 25 have been amended. New claims 26-28 have been added. Accordingly, after the foregoing amendment has been entered, claims 13-28 will be pending in this application.

Support for the amendments to the claims may be found throughout the specification and claims as originally filed. Specifically support for the amendments to claims 13, 17, 19, 21, 24, and 25 may be found at, for example, page 12, lines 5-9 of the specification; support for the amendments to claims 17-20, 24-26 may be found at, for example, page 22, lines 4-13, page 17, line 28, through page 18, line 33 of the specification; support for the amendments to claim 25 and new claims 26 and 27 may be found at, for example, page 5, lines 16-36 of the specification; and support for new claim 28 may be found at, for example, page 7, lines 14-15 of the specification. *No new matter has been added to the application by way of these amendments.*

The foregoing amendments have been made solely for the purpose of expediting prosecution of the present application and should in no way be construed as acquiescence to any of the Examiner's rejections in this or in any former Office Action issued in the present application. Applicants reserve the right to pursue the subject matter of the claims as originally filed in this application or in another related application.

Withdrawal of Certain Objections / Rejections

Applicants gratefully acknowledge the Examiner's indication that the following objection and rejections have been withdrawn:

- (a) the previous objection to claims 16 and 21-23 for use of the acronym "TNF α ";
- (b) the previous rejection of claims 13-23 under 35 U.S.C. §112, second paragraph as being indefinite for the term "and/or"; and
- (c) the previous rejection of claims 13 and 14 under 35 U.S.C. §102(b) as being anticipated by Okada, *et al.* (EP 1174148).

With respect to the Examiner's indication that the previous rejection of claims 15, 17, 18, and 19 under 35 U.S.C. §103(a) as being unpatentable over Okada, *et al.* (EP 1174148) has been

withdrawn, Applicants respectfully request clarification from the Examiner regarding this indication. Applicants note that the rejection was based on the combination of Gombotz and Okada, and appears to have been maintained as described below.

Claim Rejections Under 35 U.S.C. § 102

I. The Examiner has rejected claims 13 and 14 under 35 U.S.C. § 102(e) as allegedly being anticipated by Gombotz, *et al.* (U.S. 20030180287). Applicants respectfully traverse the foregoing rejection for the reasons set forth below.

For a prior art reference to anticipate a claimed invention, the prior art must teach each and every element of the claimed invention. *Lewmar Marine v. Barient*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Claim 13 and claim 14 (which depends therefrom), each require *a buffer system comprising citrate and phosphate*. Although Gombotz, *et al.* teach examples of individual buffers, Gombotz, *et al.* fail to teach or suggest the combination of citrate and phosphate buffers. Thus, Gombotz, *et al.* fail to teach or suggest the compositions described in claims 13 and 14. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection under 35 U.S.C. 102(e) as allegedly being anticipated by Gombotz, *et al.*

Rejection of Claims Under 35 U.S.C. §103(a)

I. The Examiner has rejected claims 15, 17, 18, and 19 under 35 U.S.C. §103(a) as being unpatentable over Okada, *et al.* (EP 1174148) and Gombotz, *et al.* (U.S. 20030180287) as applied to claims 13 and 14 above. Applicants respectfully traverse this rejection for the reasons set forth below.

The test for *prima facie* obviousness is consistent with the legal principles enunciated in *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727 (2007). *Takeda Chem. Indus., Ltd. v. Alpharma Pty., Ltd.*, 2007 U.S. App. LEXIS 15349, at *13 (Fed. Cir. 2007). “While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation (“TSM”) test, the Court acknowledged the importance of identifying ‘a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does’ in an obviousness determination. *Id.* at *13-14 (quoting KSR, 127 S. Ct. at 1731).

Although the TSM test should not be applied in a rigid manner, it can provide helpful insight to an obviousness inquiry. *KSR*, 127 S. Ct. at 1731. Furthermore, the prior art reference (or references when combined) must teach or suggest all of the claim limitations (M.P.E.P. § 2143).

As described above, amended claim 13 (from which claim 15 depends) requires *a buffer system comprising a combination of citrate and phosphate, as well as an antibody concentration of 20-130 mg/ml.* Similarly, claim 17 (from which claims 18 and 19 depend) has been amended to also specify *a buffer system comprising a combination of citrate and phosphate, and an antibody concentration of 20-130 mg/ml.*

The primary reference relied upon by the Examiner, Gombotz, *et al.*, fail to teach or suggest *a buffer system comprising the combination of citrate and phosphate*, as required by amended claims 13 and 17, and claims dependent therefrom. Furthermore, while Gombotz, *et al.* generically teach that the formulations may contain “25 to about 50 mg TNFR:Fc” (see [0050] of Gombotz, *et al.*) or “10 to about 100 mg/mL RANK:Fc” (see [0051] of Gombotz, *et al.*), notably these proteins are not antibodies, but rather fusion proteins and are described in the context of very specific formulations. Based on the foregoing, Gombotz, *et al.* fail to teach or suggest all of the claim limitations.

The teachings of the Okada, *et al.* fail to make up for the deficiencies in the primary reference of Gombotz, *et al.*.

More specifically, although Okada, *et al.* generically teaches formulations having a range of 2-100 mg of a Fab fragment, one of ordinary skill in the art would have no expectation of success or motivation to combine the teachings of this reference with Gombotz, *et al.* to achieve formulations comprising 20-130 mg/ml of an antibody. For example, Applicants direct the Examiner’s attention to the working examples of Okada, *et al.* which merely teach compositions comprising 2 mg/ml of protein. In particular, Table 1 at page 5 of Okada, *et al.* teach the preparation of formulations comprising 2 mg /ml of a Fab fragment (see, e.g., [0028] OF Okada, *et al.*); “Inventive Examples” 4-9 of Okada teach that the Fab fragment formulation contained only about 1 mg/ml of the Fab fragment which was subsequently diafiltered to 2 mg/ml (see page 6, [0030] of Okada, *et al.*); Examples 10 and 11 of Okada, *et al.* describe formulations containing 2 mg/ml of the Fab fragment (seem page 7, [0032] and [0034] of Okada, *et al.*). Thus, while at [0008] Okada, *et al.* teach that a formulation comprising a Fab fragment may contain 2-100 mg, the working examples of Okada, *et al.*

clearly demonstrate that the formulations of Okada, *et al.* comprise low amounts or protein, *i.e.*, 2 mg/ml.

Moreover, Okada, *et al.* teaches away from increasing the Fab fragment to greater than 10 mg/ml:

According to the invention, the concentration of the Fab fragment is not particularly limited, with the proviso that it is generally within such a range that a parenteral pharmaceutical composition can be provided, but is preferably from 0.01 mg/ml to 10 mg/ml, more preferably from 0.1 to 8 mg/ml. When the concentration is lower than 0.01 mg/ml, there will be a case in which its provision as a pharmaceutical preparation is difficult in reality, because the preparation becomes large in size in order to keep the concentration for expressing effective pharmacological action. Also, when the concentration is higher than 10 mg/ml, it becomes close to the saturation solubility of the fragment, thus posing a possibility of generating aggregates during preservation. (see, *e.g.*, [0009] of Okada).

Based on the foregoing, Applicants respectfully submit that one of ordinary skill in the art would have no motivation to combine or expectation of success when combining the teachings of Gombotz, *et al.* with Okada, *et al.* given that Okada, *et al.* expressly warns of increasing protein, *i.e.*, Fab fragment, to more than 10 mg/ml as this leads to instability of the formulation. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection under 35 U.S.C. 103(a) as allegedly being anticipated by Okada, *et al.* and Gombotz, *et al.*.

II. The Examiner has rejected claim 16 under 35 U.S.C. §103(a) as being unpatentable over Gombotz, *et al.* (U.S. 20030180287) in view of Salfield, *et al.* (U.S. Patent no. 6,090,382). Applicants respectfully traverse this rejection for the reasons set forth below.

Applying *KSR*, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness for at least the following reasons.

As described above, amended claim 13 (from which claim 16 depends) requires *a buffer system comprising a combination of citrate and phosphate, as well as an antibody concentration of 20-130 mg/ml.*

Gombotz, *et al.* fail to teach or suggest a buffer system comprising *the combination of citrate and phosphate*, as required by amended claim 13, and claims dependent therefrom. Accordingly, Gombotz, *et al.* fail to teach or suggest all of the claim limitations.

The teachings of the Salfield, *et al.* fail to make up for the deficiencies in the primary reference of Gombotz, *et al.*

Salfield, *et al.* teach fully human antibodies and methods of use of such antibodies. Although, Salfield, *et al.* provides general teachings regarding the formulation of such antibodies, Salfield, *et al.* fail to teach or suggest formulations of such antibodies in *a buffer system comprising a combination of citrate and phosphate or having an antibody concentration of 20-130 mg/ml*, as required by the claims.

Accordingly, the teachings of Gombotz, *et al.* and Salfield, *et al.*, either alone or in combination, fail to teach or suggest all of the claim limitations and, Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection under 35 U.S.C. 103(a) as allegedly being anticipated by Gombotz, *et al.* and Salfield, *et al.*.

III. The Examiner has rejected claims 21-24 under 35 U.S.C. §103(a) as being unpatentable over Gombotz, *et al.* (U.S. 20030180287) in view of Salfield, *et al.* (U.S. Patent no. 6,090,382). Applicants respectfully traverse this rejection for the reasons set forth below.

Applying KSR, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness for at least the following reasons.

Amended claim 17 (from which claims 21-24 depend) requires *a buffer system comprising a combination of citrate and phosphate buffer, in addition to an antibody concentration of 20-130 mg/ml*.

Gombotz, *et al.*, fail to teach or suggest *a buffer system comprising the combination of citrate and phosphate*, as required by amended claims 13 and 17, and claims dependent therefrom. Accordingly, Gombotz, *et al.* fail to teach or suggest all of the claim limitations.

The teachings of the Salfield, *et al.* fail to make up for the deficiencies in the primary reference of Gombotz, *et al.*

Salfield, *et al.* teach fully human antibodies and methods of use of such antibodies. Although, Salfield, *et al.* provides general teachings regarding the formulation of such antibodies, Salfield, *et al.* fail to teach or suggest formulations of such antibodies in *a buffer*

system comprising a combination of citrate and phosphate or having an antibody concentration of 20-130 mg/ml, as required by the claims.

Accordingly, the teachings of Gombotz, *et al.* and Salfeld, *et al.*, either alone or in combination, fail to teach or suggest all of the claim limitations and Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection under 35 U.S.C. 103(a) as allegedly being anticipated by Gombotz, *et al.* and Salfeld, *et al.*

New Rejections

Objection to the Claims

The Examiner has objected to claim 24 for the term “polysorbate 80” being underlined.

Applicants respectfully submit that amendment of claim 24 to remove the underline by deleting the term “polysorbate 80” and adding the term “polysorbate 80” has rendered the Examiner’s objection moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of the objection to claim 24.

The Examiner has objected to claim 25 for the term “mg/mL.”

Applicants respectfully submit that amendment of claim 25 to recite “mg/ml” has rendered the Examiner’s objection moot. Accordingly, Applicants respectfully request reconsideration and withdrawal of the objection to claim 25.

Rejection of Claims Under 35 U.S.C. §112, First Paragraph-New Matter

The Examiner has rejected claim 17 under 35 U.S.C. § 112, first paragraph, as allegedly “containing new matter” for the phrase “about 0 to about 15 mg/ml of polysorbate 80.”

Applicants respectfully traverse the foregoing rejection for the following reasons. According to M.P.E.P. § 2163, when a disclosure describes a claimed invention in a manner that permits one of ordinary skill in the art to reasonably conclude that the inventor possessed the claimed invention at the time of filing of the application, the written description requirement is

satisfied. This possession may be shown in any number of ways and an Applicant need not describe every claim feature exactly because *there is no in haec verba requirement.* (M.P.E.P. § 2163). Rather, to satisfy the written description requirement, all that is required is “reasonable clarity.” (M.P.E.P. § 2163.02). In addition, *an adequate description may be made in any way through express, implicit, or even inherent disclosures in the application, including words, structures, figures, diagrams, and/or formulae.* (M.P.E.P. §§ 2163(I), 2163.02).

In the present case, based on the teachings in Applicants’ specification, one of ordinary skill in the art would readily understand that the formulations taught in the specification may not contain a surfactant, such as Polysorbate-80, e.g., the formulations comprise 0 mg/ml of Polysorbate-80. Accordingly, at the time of the invention, one of ordinary skill in the art would readily conclude that Applicants were in possession of formulations that do not contain a surfactant.

Nevertheless, without acquiescing to the Examiner’s rejection and solely in the interest of expediting prosecution of the application, Applicants have amended claim 25, thereby rendering the Examiner’s rejection moot.

The Examiner has rejected claim 25 under 35 U.S.C. § 112, first paragraph, as allegedly “containing new matter” for the term “Adalimumab.”

Applicants respectfully submit that based on the teachings in Applicants’ specification in combination with the knowledge in the art at the time of the invention, one of ordinary skill in the art would readily conclude that Applicants were in possession of antibodies that are Adalimumab at the time of the invention, as required by 35 U.S.C. § 112, first paragraph. Nevertheless, without acquiescing to the Examiner’s rejection and solely in the interest of expediting prosecution of the application, Applicants have amended claim 25, thereby rendering the Examiner’s rejection moot.

Rejection of Claims Under 35 U.S.C. §103(a)

The Examiner has rejected claim 25 under 35 U.S.C. §103(a) as being unpatentable over Gombotz, *et al.* (U.S. 20030180287) in view of Salfield, *et al.* (U.S. Patent no. 6,090,382). Applicants respectfully traverse this rejection for the reasons set forth below.

Applying *KSR*, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness for at least the following reasons.

Claim 25, as amended, requires a buffer comprising a combination of a citrate and phosphate, in addition to an antibody concentration of 20-130 mg/ml.

Gombotz, et al., fail to teach or suggest *a buffer system comprising the combination of citrate and phosphate*, as required by amended claim 25, and claims dependent therefrom. Accordingly, Gombotz, et al. fail to teach or suggest all of the claim limitations.

The teachings of the Salfield, et al. fail to make up for the deficiencies in the primary reference of Gombotz, et al.

Salfield, et al. teach fully human antibodies and methods of use of such antibodies. Although, Salfield, et al. provides general teachings regarding the formulation of such antibodies, Salfield, et al. fail to teach or suggest formulations of such antibodies in *a buffer system comprising a combination of citrate and phosphate or having an antibody concentration of 20-130 mg/ml*, as required by the claims.

Accordingly, the teachings of Gombotz, et al. and Salfield, et al., either alone or in combination, fail to teach or suggest all of the claim limitations and Applicants respectfully request that the Examiner reconsider and withdraw the foregoing rejection under 35 U.S.C. 103(a) as allegedly being anticipated by Gombotz, et al. and Salfield, et al.

SUMMARY

If a telephone conversation with Applicant's Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 449-6500.

The Commissioner is hereby authorized to charge any fees associated with the filing of this communication to our Deposit Account No. 50-4876, under Order No. 117813-16602 from which the undersigned is authorized to draw.

Dated: February 1, 2010

Respectfully submitted,

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